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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,429	12/03/2001	Vincent Sewalt	5718-119 (035718/241421)	8554

826 7590 06/30/2004

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EXAMINER

BAUM, STUART F

ART UNIT PAPER NUMBER

1638

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/005,429	Applicant(s) SEWALT ET AL.	
	Examiner Stuart F. Baum	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 62-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 62-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/10/03, 9/17/03, 3/26/02</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election without traverse of Group IV, claims 23, 30, 36, 46, and 53 including SEQ ID NO:13 encoding SEQ ID NO:14 and SEQ ID NO:24 encoding SEQ ID NO:25 in the reply filed on April 19, 2004 is acknowledged.

Claims 62-94 are pending.

Claims 1-61 have been canceled.

Claims 62- 94 have been newly added and are drawn to the subject matter recited in the elected Group IV.

2. Claims 62-94 are examined in the present office action.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See for example page 23, line 15. See MPEP § 608.01.

Claim

4. Claim 72, line 2, is objected to for reciting "plant corn" instead of "corn plant".
Correction is requested.

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Written Description

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 62-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods and a plant comprising transforming a plant with a first nucleotide sequence and a second nucleotide sequence wherein the first nucleotide sequence encodes any NADPH-thioredoxin reductase, or wherein the nucleotide sequence hybridizes under stringent conditions to the sequence as set forth in SEQ ID NO:24 or a nucleotide sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO:24, and wherein the second nucleotide sequence encodes any thioredoxin h, or wherein the second nucleotide sequence hybridizes to the sequence set forth in SEQ ID NO:13 under stringent conditions, or wherein the second nucleotide sequence has at least 95% sequence identity to the sequence set forth in SEQ ID NO:13.

Applicants only disclose the nucleotide sequences set forth in SEQ ID NO:24 or 13.

The Applicants do not identify essential regions of the NADPH-thioredoxin reductase or the thioredoxin h proteins encoded by SEQ ID NO:24 and 13, respectively, any polynucleotide sequences that hybridize to SEQ ID NO:24 or 13, nor any sequences that have at least 95%

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sequence identity to SEQ ID NO:24 or 13 and encode a protein with the same activity as a NADPH-thioredoxin reductase encoded by SEQ ID NO:24 or a protein with the same activity as a thioredoxin h encoded by SEQ ID NO:13. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicants fail to describe a representative number of polynucleotide sequences encoding a NADPH-thioredoxin reductase or a thioredoxin h protein falling within the scope of the claimed genus of polynucleotides which hybridize to SEQ ID NO:24 or 13 or which are at least 95% sequence identical to SEQ ID NO:24 or 13. Applicants only describe a single sequence of SEQ ID NO:24 and a single sequence of SEQ ID NO:13. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for the NADPH-thioredoxin reductase or thioredoxin h proteins, it

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remains unclear what features identify a NADPH-thioredoxin reductase or a thioredoxin h protein. Since the genus of NADPH-thioredoxin reductase or a thioredoxin h proteins have not been described by specific structural features, the specification fails to provide an adequate written description to support the breadth of the claims.

Scope of Enablement

6. Claims 62-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for decreasing the number of disulfide bonds of storage proteins in a plant or part thereof comprising transforming a plant with a nucleotide sequence comprising SEQ ID NO:24 encoding a NADPH-thioredoxin reductase and a nucleotide sequence comprising SEQ ID NO:13 encoding a thioredoxin h wherein the expression of both nucleotide sequences in grains chemically reduces the disulfide bonds of storage proteins, and a plant transformed with said nucleotide sequences, does not reasonably provide enablement for claims drawn to a method for altering the disulfide status of storage proteins in a plant or part thereof, wherein the hardness of a grain is increased, a method for improving the digestibility of grain, a method for improving grain processing and a transformed plant comprising transforming a plant with a first and second nucleotide sequence encoding any NADPH-thioredoxin reductase and thioredoxin h, respectively, or wherein the first nucleotide sequence comprises SEQ ID NO:24 or has at least 95% sequence identity to SEQ ID NO:24 or hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:24 or the second nucleotide sequence comprises SEQ ID NO:13 or has at least 95% sequence identity to SEQ ID NO:13 or hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:13. The specification

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does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a method for altering the disulfide status of storage proteins in a plant or part thereof wherein the hardness of a grain is increased, a method for improving the digestibility of grain, a method for improving grain for processing or a transformed plant comprising transforming a plant with a nucleic acid sequence encoding any NADPH-thioredoxin reductase, a nucleic acid sequence comprising SEQ ID NO:24 or wherein the nucleotide sequence hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:24 or is 95% sequence identical to the sequence set forth in SEQ ID NO:24 and comprising transforming said plant with a nucleic acid sequence encoding any thioredoxin h, a nucleic acid sequence comprising SEQ ID NO:13, or wherein the nucleotide sequence hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:13, or is 95% sequence identical to the sequence set forth in SEQ ID NO:13, wherein the nucleotide sequences are

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operably linked to a promoter, wherein the processing is wet milling, grinding, steam flaking or dry grind ethanol production.

Applicants transformed maize plants with a nucleic acid sequence of SEQ ID NO:24 encoding a NADPH-thioredoxin reductase and a nucleic acid sequence of SEQ ID NO:13 encoding thioredoxin h, both of which are operably linked to a Gamma zein promoter (page 43, lines 17 to 23). Applicants analyzed transformed plants by grinding corn kernels and treating the ground corn with 1 mM dithiothreitol (DTT) versus a control which was not treated with DTT. Applicants report that enzyme digestible dry matter percent (EDDM%) of the grain was measured using the method of Boisen and Fernandez (page 44, lines 10-13) and report that this method is a measure of digestibility (page 51, line 24). Applicants purport that the digestibility of kernels overexpressing both NADPH-thioredoxin reductase and thioredoxin h is increased significantly compared to kernels from wild-type plants (page 54, lines 15-18).

Applicants claim methods for altering the disulfide status of storage proteins, improving the digestibility of grain and improving grain processing but Applicants have presumably only reduced the number of disulfide bonds in corn kernels. Applicants have not increased the number of disulfide bonds, or improved the digestibility or grain processing of corn kernels. Applicants have not stated the relationship between the EDDM% assay and digestibility and processing of grains. Applicants report that "digestibility" is defined as the fraction of feed or food that is not excreted as feces, or defined as digestibility of specific components such as energy or protein measured by determining the concentration of these components in foodstuffs and in the excreta. (page 11, lines 7-10). In addition, digestibility and processing also include breaking down cell walls. It is not clear how Applicants can claim methods of improving

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digestibility and processing of grains when Applicants have not measured animal excreta from animals that have been fed Applicants' transformed maize plants or kernels or analyzed the processing characteristics of said maize plants or kernels.

The state-of-the-art is such that one of skill in the art cannot predict which nucleic acids that are 95% sequence identical to SEQ ID NO:24 or 13, or sequences that hybridize under stringent conditions to SEQ ID NO:24 or 13 will encode a protein with the same activity as a protein encoded by SEQ ID NO:24 or 13. The prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex, and the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited (Bowie et al, Science 247:1306-1310, 1990, see especially page 1306). Proteins may be sensitive to alterations in even a single amino acid in a sequence. For example, the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain (McConnell et al, Nature 411 (6838):709-713, 2001, see especially page 710, left column, 2nd paragraph).

Applicants have not disclosed how one makes or isolates any of the sequences that are encompassed by Applicants' broad claims. Applicants have not taught which regions of the respective polynucleotides can be used to amplify any of said polynucleotides or which regions can be used as a probe to isolate any of said polynucleotide sequences.

Applicants' recitations of "altering the disulfide status", "improving the digestibility of grain" and "improving grain for processing" read on both increases and decreases in disulfide

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bonds. In regards to increasing the number of disulfide bonds by utilizing antisense and co-suppression technology, Applicants are not enabled. The state-of-the-art teach that sense and antisense constructs can behave unpredictably when transformed into a plant. Colliver et al (1997, Plant Mol. Biol. 35:509-522) showed that transformation of bird's foot trefoil with a construct that was antisense to bean chalcone synthase unexpectedly resulted in transformants with *increased* levels of chalcone synthase transcripts (page 519, left column, 2nd paragraph). Montgomery et al (Trends in Genetics, July 1998, 14(7):255-258) teach that not all transgenes can cause co-suppression in plants and that there is no basis for predicting which transgenes would have this effect (page 257, column 1, last paragraph).

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of SEQ ID NO:24 or 13 as probes or by designing primers to undisclosed regions of SEQ ID NO:24 or 13 and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed reduce disulfide bonds in storage proteins and hybridize under stringent conditions to SEQ ID NO:24 or 13 or exhibit at least 95% sequence identity with SEQ ID NO:24 or 13.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 62-94 are rejected under 35 U.S.C. 102(e) as being anticipated by Lanahan (December, 1998, WO 00/36126).

The claims are drawn to a method for altering the disulfide status of storage proteins in a plant or part thereof, a method for improving the digestibility of grain, a method for improving grain for processing or a transformed plant comprising transforming a plant with a nucleic acid sequence encoding any NADPH-thioredoxin reductase or wherein the nucleotide sequence hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:24 and comprising transforming said plant with a nucleic acid sequence encoding any thioredoxin h or wherein the nucleotide sequence hybridizes under stringent conditions to the nucleotide sequence set forth in SEQ ID NO:13, wherein said part is a seed or grain, wherein the nucleotide sequences are operably linked to a constitutive, tissue preferred, or chemically regulated promoter, wherein said digestibility of said grain is increased when consumed by a ruminant or monogastric animal, wherein the grain is a maize kernel, wherein the grain is a kernel that is part of a whole corn plant harvested for silage, wherein the processing is wet milling, grinding, steam flaking or dry grind ethanol production, wherein the plant is a maize or soybean plant, or seed from the transformed plant.

Lanahan teaches a method of reducing the disulfide bonds in seed proteins and a plant comprising transforming corn or soybean plants with a nucleic acids encoding thioredoxin and thioredoxin reductase operably linked to a promoter and a plant comprising said sequences

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(pages 1-3, and page 34-35, claims 1-13). The Office interprets “thioredoxin h” and “thioredoxin” to be the same enzymes and have the same activity. Because Applicant does not specify under which specific conditions a nucleotide sequence would hybridize to SEQ ID NO:24 or 13, the Office interprets “stringent conditions” to mean low stringent conditions, and as such, the sequences of Lanahan would hybridize to Applicants’ SEQ ID NO:24 and 13. Lanahan also teaches that the promoter can be a constitutive promoter, a chemically-inducible promoter or a seed specific promoter (See page 11, lines 30-41, for example). The Office interprets a “seed specific” promoter to encompass a tissue preferred promoter. Lanahan discloses that the grain performance in livestock feed is increased (page 1, lines 19-22). The Office interprets the recitation “livestock” as recited on page 1, line 20, to encompass ruminant or monogastric animals. The Office interprets the recitation “grain” to include maize kernels or soybean seeds as is recited in claims 1-3 (See page 34). Because Applicants’ methods and plant all comprise the same starting materials and methods steps, and if the methods of Lanahan also improve digestibility and processing of grains, then Lanahan anticipates the claimed invention. In addition, because the grain processing procedures, i.e., wet milling, grinding, steam flaking or dry grind ethanol production, all comprise the same starting materials and method steps as taught by Applicant, it would be inherent that the method of Lanahan would also improve the same grain processing procedures as taught by Applicant; and as such, Lanahan anticipates the claimed invention.

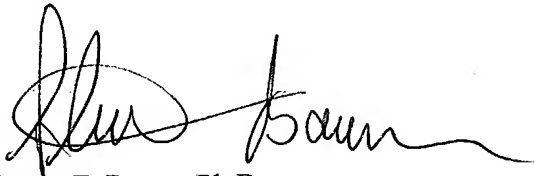
8. No claims are allowed.

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9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

A handwritten signature in black ink, appearing to read 'Stuart F. Baum', with a stylized, cursive script.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
June 23, 2004